REMARKS

Upon entry of this amendment, claims 56, 59, 60, 67-69 and 105-108 are under examination. Applicants have amended claim 59 to correct lack of antecedent basis for the term "depletory". Support for these amendments can be found in the instant specification and claim as filed. No new matter is added.

The Examiner has withdrawn claims 70-77 for being drawn to non-elected species. Applicants submit that claim 56 is a linking claim for the species of the invention and is being examined with the elected invention. When all claims directed to the elected invention are allowable, should any linking claim be allowable, the restriction requirement between the linked inventions must be withdrawn. Any claim(s) directed to the non-elected inventions, previously withdrawn from consideration, which depends from or requires all the limitations of the allowable linking claim must be rejoined and will be fully examined for patentability.

Claims 1-55, 57, 58, 61-66 and 78-104 have been cancelled for being drawn to non-elected subject matter. Applicants reserve the right to pursue the subject matter of these claims in a divisional application.

Rejections under 35 U.S.C. § 103.

The Examiner has rejected claims 56-60, 67-69 and 105-108, on pages 6-7 of the Office Action, for obviousness over McInnes *et al.* Immunol. Today 19(2):75-9 (Feb. 1998) ("McInnes 1998" or "McInnes #1") in light of Ledbetter *et al.* U.S. Publication No. 2003-0118592 ("Ledbetter") and McInnes *et al.* Nat Med. 3(2):198-95 (Feb. 1997) ("McInnes 1997" or "McInnes #2"). Applicants have canceled claims 57 and 58, so this rejection is moot as it regards these claims.

The Examiner argued that McInnes 1998 teaches that IL-15 mediates recruitment and activation of T cells from the peripheral blood in rheumatoid arthritis patients and that T cells in these patients have upregulated CD69 expression. The Examiner asserted that McInnes 1998 did not teach the use of a depleting anti-CD69 antibody to treat rheumatoid arthritis.

The Examiner further argued that Ledbetter teaches human and humanized anti-CD69 antibodies effective in the depletion of immune cells, as well as toxin conjugated antibodies.

Further, the Examiner asserted that Ledbetter teaches that autoreactive T and B cells are present in rheumatoid arthritis patients and that anti-CD69 antibodies can be used to treat various autoimmune diseases and tumors.

Moreover, the Examiner asserted that McInnes 1997 teaches that anti-CD69 antibody blocks IL-15 activated T cell production and induction of TNFα in macrophages and monocytes. The Examiner argued that given the teachings of McInnes 1998 it would have been obvious to one of ordinary skill in the art that an excellent alternative to neutralizing IL-15 would have been to treat rheumatoid arthritis by depleting CD69 expressing T-cells with an anti-CD69 antibody as taught by Ledbetter. The Examiner further argued that even if the anti-CD69 antibody would not have depleted the CD69 T-cells, the teachings of McInnes 1997 show that anti-CD69 antibodies would at least prevent the T cells from producing TNFα. Applicants traverse the rejection for the reasons detailed below.

Applicants submit that claims 56, 59, 60, 67-69 and 105-108 are not obvious over McInnes 1998, in light of Ledbetter and McInnes 1997. First, Applicants argue that the Examiner is using an impermissible obvious to try standard. Second, Applicants show that there is no motivation to combine the teachings of McInnes 1998, Ledbetter and McInnes 1997. Third, Applicants assert that the methods of claims 56, 59, 60, 67-69, and 105-108 are based upon unexpected results so that one of ordinary skill in the art would not have a reasonable expectation of success in the methods of the instant claims in light of the teachings of McInnes 1998, Ledbetter and McInnes 1997.

Impermissible Use of the Obvious to Try Standard.

The Examiner is using an impermissible obvious to try standard in the rejection of claims 56, 59, 60, 67-69 and 105-108 over the teachings of McInnes 1998, Ledbetter and McInnes 1997. Obvious to try is not the standard under 35 U.S.C. § 103.[1] What is obvious to try would be to try each of numerous choices until one possibly arrived at a successful result or explore a new technology or general approach that seemed to be a promising field of experimentation.[2] The teachings of McInnes 1998, Ledbetter and McInnes 1997 taken together, present numerous choices to be tried, but do not lead one of ordinary skill in the art to a successful result.

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[1] MPEP § 2145.
[2] *Id.*

McInnes 1998 teaches that IL-15 can both recruit and expand CD45R0+ memory T-cells subsets in the synovial membrane which in the continued presence of IL-15 or via contact with macrophages, increase production of TNFα.[3] To remedy this, McInnes 1998 teaches that IL-15 expression should be downgraded or IL-15 receptors should be targeted in order to decrease inflammation.[4] No animal study data was shown in the teachings of McInnes 1998. Thus, McInnes 1998 does not disclose and does not enable a method of treating a subject with a depleting anti-CD69 antibody molecule of the claims.

McInnes 1997 teaches that peripheral blood T-cells and U937 cells that are co-cultured in the presence of IL-15 *in vitro* have decreased TNFα production when treated with an antibody to CD69.[5] There are no teachings in McInnes 1997 that these antibodies deplete the cultures of $CD69^+$ cells. No animal study data was shown in the teachings of McInnes 1997. Thus, McInnes 1997 does not disclose and does not enable a method of treating a subject with a depleting anti-CD69 antibody molecule of the claims.

Furthermore, contrary to the examiner's assertion that the McInnes references "point on of ordinary skill in the art to three targets: the IL-15 ligand, the IL-15 receptor and CD69," nowhere does the references limit potential therapeutic target to this list and nowhere in these references is CD69 referred to as a therapeutic target. Indeed, in the concluding section of McInnes 1998 under the heading *Therapeutic implications*, CD69 is not even mentioned. IL-15 is highlighted as the target. Specifically, McInnes 1998 states as follows:

> The identification of IL-15-mediated T-cell and monocyte activation in synovial membrane, apparently operating upstream from the effects of TNF-α, provides a novel target for such biological therapeutic approaches. This might be either through direct neutralization of IL-15 or by targeting IL-15 receptors, particularly IL-15Rα. Studies in animal models of arthritis are now required to address these exciting possibilities.

Thus, McInnes 1998 merely suggests IL-15 or one of the multitudes of IL-15 receptors as potential therapeutic targets.

McInnes 1997 also does not identify CD69 as a therapeutic target. McInnes 1997 reports to role of IL-15 in the induction of TNFα production in rhematoid arthritis through activation of

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[3] *See* McInnes #1 at page 77, column 1, first full paragraph.
[4] *Id.* at page 78, column 2, first full paragraph.
[5] *See* McInnes 1997 at page 192, column 2, first full paragraph.

synovial T cells, which often express CD69, HLA-DR, and VLA1.[6] The experimental result in McInnes 1997 show that antibodies against CD69, LFA-1, and ICAM-1 significantly inhibited the ability of T cells to activate macrophages by cell contact, thereby implicating IL-15 as the source of the induction of TNFα production as opposed to other cytokines such as IL-2. CD69 is identified as a participant in the IL-15 molecular pathways, however, CD69 is not taught as a potential therapeutic target. Indeed, McInnes 1997 concludes with a list of implications of the results that in no way discloses CD69 as a potential target; all focus is placed on IL-15. This conclusion is evidenced by the fact that McInnes 1998, a review article published a year after McInnes 1997 (see excerpt above), fails to expressly identify CD69 as a therapeutic target. Thus, even with the benefit of the data set forth in McInnes 1997, the main authors of McInnes 1997 failed to identify CD69 as a potential therapeutic target.

Ledbetter does not cure the deficiencies of the McInnes references. Ledbetter teaches binding domain immunoglobulin fusion proteins.[7] Specifically, Ledbetter teaches "binding domain-immunoglobulin fusion proteins that feature a binding domain for a cognate structure such as an antigen, a counterreceptor or the like, a wild-type IgG1, IGA or IgE hinge region polypeptide or a mutant IgG1 hinge region polypeptide having either zero, one or two cysteine residues, and immunoglobulin CH2 and CH3 domains, and that are capable of ADCC and/or CDC while occurring predominantly as polypeptides that are compromised in their ability to form disulfide-linked multimers."[8] The antigen of the binding domain-immunoglobulin fusion protein of Ledbetter may be any one of CD19, CD20, CD22, CD37, CD40, L6, CD2, CD28, CD30, CD40, CD50 (ICAM3), CD54 (ICAM1), CD80, CD86, B7-H1, CD134 (OX40), CD137 (41BB), CD152 (CTLA-4), CD153 (CD30 ligand), CD154 (CD40 ligand), ICOS, CD19, CD3, CD4, CD25, CD8, CD11b, CD14, CD25, CD56, and CD69.[9] Ledbetter fails to set forth with any specificity a CD69 antibody. Further, no where are the binding domain-immunoglobulin fusion proteins of Ledbetter described as depleting antibodies.

The examiner maintains in the Office Action at page 4 that "[a]s essentially stated in the prior Office Action of February 5, 2007, Ledbetter teaches human and humanized anti-CD69

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[6] See McInnes 1997 at abstract and page 192, right column, last paragraph.
[7] See Ledbetter at the Abstract.
[8] *Id.*
[9] See *e.g.*, *Id.* at claim 17.

antibodies with enhanced antibody dependent cell cytotoxicity and complement fixation activity, both of which lead to effective depletion of immune cells." The Office Action of February 5, 2007 at page 6 explains as follows:

> Ledbetter teaches human and humanized anti-CD69 antibodies with enhanced antibody dependent cell cytotoxicity and complement fixation activity, both of which lead to effective depletion of immune cells, such as B cells and T cells (see entire document, in particular pages 4-5, paragraphs [0021]-[0029], page 14, paragraph [0105] and claims 17 and 35). Ledbetter further teaches that radiolabeled antibodies and toxin conjugated antibodies are effective for treating tumors, such as B cell tumors (see in particular, pages 2-4, paragraphs [0011]-[0019]).

Applicants respectfully submit that Ledbetter at the pages 4-5, paragraphs [0021]-[0029] predominately provides a discussion related to CD20 antibodies. Ledbetter at the page 14, paragraph [0105] list several binding domain polypeptides and antigens, one of which is CD69. Claims 17 and 35 provide a similar list. Ledbetter at pages 2-4, paragraphs [001]-[0019] provides a general discussion of immunoglobulin therapy. The examiner's reliance on these disclosures is not well understood by Applicants. Contrary to the examiner's assertion, nowhere in these passages are human or humanized anti-CD69 antibodies expressly disclosed. Further, as indicated above, the focus of Ledbetter is on B cell depletion therapy, not CD69 depletion. [10]

Furthermore, the examiner's rationale for equating cell cytotoxicity and complement fixation activity disclosed in Ledbetter with the recited depleting activity in unclear and is not supported by proper documentary evidence. Official notice unsupported by documentary evidence should only be taken by the examiner where the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known. M.P.E.P. § 2144.03 (A). Applicants respectfully submit that Ledbetter fails to teach a depleting anti-CD69 antibody and that the documentary evidence does not support such a conclusion.

Rather, Ledbetter merely teaches various cell surface antigens that may be targeted by the binding domain immunoglobulin fusion proteins.[11] One of these many proteins is CD69.[12] No specific data regarding the production of antibodies or antibody-like molecules that specifically

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[10] *Id.* at paragraph 137.
[11] *Id.* at paragraph 105.
[12] *Id.*

bind to CD69 are mentioned, or antibodies or antibody-like molecules that deplete CD69+ cells. Ledbetter mentions rheumatoid arthritis in a list of several pathologies, that may be amenable to treatment using the myriad of antibodies or antibody-like molecules that specifically bind to one of many cell surface antigens, which may be any one of CD19, CD20, CD22, CD37, CD40, L6, CD2, CD28, CD30, CD40, CD50 (ICAM3), CD54 (ICAM1), CD80, CD86, B7-H1, CD134 (OX40), CD137 (41BB), CD152 (CTLA-4), CD153 (CD30 ligand), CD154 (CD40 ligand), ICOS, CD19, CD3, CD4, CD25, CD8, CD11b, CD14, CD25, CD56, and CD69 .[13]

Applicants assert that a person having ordinary skill in the art, reviewing the combination of McInnes 1998, Ledbetter, and McInnes 1997 would have to try each of numerous choices until he or she possibly arrived at a successful result. McInnes 1998 and McInnes 1997 at most identify IL-15 and the several IL-15R as possible therapeutic targets. Ledbetter teaches antibody and antibody-derived molecules that bind to many cell surface antigens for the treatment numerous pathologies. From these teachings, one of ordinary skill in the art would have to choose between various agents that decrease expression of IL-15, decrease the activity of IL-15, various antibodies that bind specifically to CD69 and decrease expression of TNFα, as well as depleting anti-CD69 antibodies as possible therapies for various immune conditions including rheumatoid arthritis. Applicants submit that a person having ordinary skill in the art would have to try each of these numerous choices, and would have to choose the least researched choice in order arrive at the successful result of the instant claims.

No Motivation to Combine the References

Applicants assert that one of ordinary skill in the art would not have had motivation to combine the teachings of McInnes 1998 with Ledbetter, nor would they have had motivation to combine the teachings of McInnes 1997 and Ledbetter. One of the requirements to make a *prima facie* case for obviousness is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.[14]

One of ordinary skill in the art could not find a motivation to combine McInnes 1998 with Ledbetter either in the references themselves or in knowledge generally available in the art.

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[13] *Id.* at paragraphs 137-148.
[14] MPEP § 2142

McInnes 1998 teaches that CD69 is involved with IL-15 in the reduction of TNFα production by interacting with synovial T-cells. McInnes 1998 does not teach anything regarding the treatment of rheumatoid arthritis with depleting anti-CD69 antibodies. McInnes 1998 suggests that rheumatoid arthritis may be treated through the reduction of expression or activity of IL-15. McInnes 1998 does not teach or suggest that the depletion of CD69+ cells would be an effective treatment for rheumatoid arthritis. Thus, one of ordinary skill in the art would not be motivated to combine Ledbetter which teaches various depleting antibodies and related molecules for a large number of cell surface antigens, including CD69.

Likewise, one of ordinary skill in the art would not have had motivation to combine McInnes 1997 and Ledbetter. McInnes 1997 teaches that antibodies that bind CD69, but do not deplete CD69+ positive cells, reduce the amount of TNFα produced in *in vitro* co-cultures. There is no teaching that depleting CD69 antibodies are used to decrease TNFα production. McInnes 1997 does not teach that the depletion of CD69+ cells would be an effective treatment for rheumatoid arthritis. Thus, one of ordinary skill in the art would have had motivation to combine McInnes 1997 with Ledbetter which teaches various depleting antibodies and related molecules for a large number of cell surface antigens, including CD69.

Applicants further submit that the Examiner has merely asserted that a skilled artisan would have been motivated to combine the above references without identifying where in the references either explicit or implicit motivation can be found to support the rejection. Thus, the Examiner has only alleged that the references can be combined to arrive at the present invention. The mere fact that references can be combined or modified, however, does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See M.P.E.P. § 2143.01 (III). That is, a rejection based on a *prima facie* case of obviousness is improper without a motivation to combine the references. The Office Action combines facts and attempts to provide a motivation to combine the references without identifying the source of the motivation. The desirability of the combination is not suggested in any of the references cited by examiner. Accordingly, the Office Action has also failed to establish a *prima facie* case of obviousness because the cited references do not provide either explicit or implicit motivation to combine or modify the teachings of the references to arrive at the present invention.

Deputy Commissioner of Patent Operations issued a memorandum on May 3, 2007 following the Supreme Court decision on *KSR Int'l Co. v. Teleflex, Inc.* (see Exhibit A) stating the following:

> [I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

The rationale set forth by the examiner simplifies the facts and forces a wrong conclusion. KSR featured rather simple technology -- an adjustable throttle pedal for an automobile. Adjustable pedal technology accommodates an automobile throttle to drivers of different heights. The technology here is closer to the facts in Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1360 (Fed. Cir. 2007)(citations omitted), where the Federal Circuit stated as follows:

> The KSR Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." KSR, 127 S. Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

As in Takeda, the prior art, Ledbetter, discloses a broad selection of compounds any one of which could have been selected. None of the references cited by examiner provides any evidence, negative or otherwise, that would lead one of ordinary skill in the art to the present invention. Accordingly, Applicants respectfully submit that this case also fails present the type of situation contemplated by the KSR Court when it stated that an invention may be deemed obvious if it was "obvious to try."

In light of the above, Applicants respectfully submit that the Office Action fails to present sufficient reason why a person of ordinary skill in the art would have combined the teachings of McInnes 1998 with Ledbetter or McInnes 1997 with Ledbetter.

No Reasonable Expectation of Success and Unexpected Results.

Applicants assert that a person having ordinary skill in the art reviewing the cited references would not have had a reasonable expectation of success at arriving at the methods of claims 56, 59, 60, 67-69 and 105-108, in part, because of the methods of the claims are based on unexpected results. Claims 56, 59, 60, 67-69 and 105-108 are presently being examined insofar as they encompass methods of treating rheumatoid arthritis.

One of ordinary skill in the art would not have a reasonable expectation of success regarding the methods of claims 56, 59, 60, 67-69 and 105-108 based on the teachings of McInnes 1998, Ledbetter, or McInnes 1997. None of McInnes 1998, Ledbetter, or McInnes 1997 shows any *in vivo* data from animal models for arthritis. The teachings of McInnes 1998, Ledbetter and McInnes 1997 have no specific evidence regarding the efficacy of depleting anti-CD69 antibodies. The law requires that in order to qualify as prior art, a reference, or combination of references, must enable all elements of the claimed invention. See *e.g.*, Elan Pharm., Inc. v. Mayo Foundation for Medical and Education Research, 346 F.3d 1051, 1054, (Fed. Cir. 2003) and In re Donohue, 766 F.2d 531, 534 (Fed. Cir. 1985). None of the cited references teaches a specific depleting anti-CD69 antibody, or shows any evidence of their efficacy in any context.

Applicants have reviewed the examiner's analysis of the cited references Feng *et al.*, Lauzurica *et al.*, and Nakayama *et al.* and can not agree that any of these references support the examiner's conclusion that the above references render the present claims obvious. As explained by the examiner, Sancho *et al.* reports on the **"somewhat contradictory *in vitro* and *in vivo* results."** Specifically, Sancho *et al.* at page 137, top left column, references Feng *et al.*, Nakayama *et al.,* and Lauzurica *et al.* and in the following passage:

> Despite the *in vitro* evidence suggesting a possible proinflammatory role for CD69, constitutive expression of CD69 by T cells in transgenic mice is not associated with inflammatory conditions. [Feng *et al.* and Nakayama *et al.*] Furthermore, analysis of antigen-specific response in mice has not revealed reduced T-Cell activation in the absence of CD69 [Lauzurica *et al.*], suggesting that this receptor does not exert a net positive co-stimulatory effect in T cells *in vivo*, although a redundant role as a positive co-stimulus for T cells cannot be ruled out.

The examiner does not disagree with these conclusions of Sancho et al., but argues on pages 7 and 8 of the Office Action that these teachings **"do not particularly contradict"** the

teachings of McInnes 1998 and McInnes 1997. While these teachings "do not particularly contradict" the teachings of McInnes 1998 and McInnes 1997, they do no particularly support the examiner's conclusion that one of ordinary skill in art could have easily relied on the teachings these references to arrive at the present invention. Indeed, the examiner's analysis of Feng *et al.* and Lauzurica *et al.* highlights the complexities of the art and bolsters Applicants position that a person of ordinary skill in the art would not have had a reasonable expectation of success to practice the claimed invention. Applicants respectfully maintain that one of ordinary skill in the art would not have a reasonable expectation of success in the methods of the instant claims in light of the teachings of McInnes 1998, Ledbetter and McInnes 1997.

Further, Applicants respectfully submit that the examiner is carefully navigating the complexities of the art with the benefits of hindsight to arrive at the present invention and, moreover, understates the significance of the data presented in the specification. The instant specification shows for the first time *in vivo* treatment of collagen induced arthritis (CIA) in mice with anti-CD69 antibody.[15] CIA is a widely accepted experimental model of inflammatory joint disease and specifically rheumatoid arthritis.[16] McInnes 1998, Ledbetter, or McInnes 1997 show no experimental evidence of any sort that suggests that CD69 depleting antibodies work to alleviate the symptoms of rheumatoid arthritis. As explained above, they merely invite one of ordinary skill in the art to try many options to arrive at the claimed invention. Thus, Applicants submit that without any data on point of any kind, and previously published contradictory *in vivo* data, the teachings of McInnes 1998, Ledbetter, and McInnes 1997 alone or in combination provide no reasonable expectation of success to one of ordinary skill in the art.

The invention of claims 56, 59, 60, 67-69 and 105-108 is also based on unexpected results, which is evidence that the methods of these claims are non-obvious over McInnes 1998, Ledbetter, and McInnes 1997. The specification teaches, unexpectedly from the standpoint of one of ordinary skill in the art at the time the invention was made, that it is important that the CD69 specific antibody be a depletor of CD69+ cells, as opposed to specifically binding to CD69, while not depleting CD69+ cells. Treatment of CIA induced mice with mAb 2.2, a CD69 specific antibody that does not deplete CD69+ cells *in vivo*, exacerbated CIA in those mice.[17]

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[15] *See* the instant specification from page 104, line 14 to page 106, line 2.
[16] *Id.* from page 30, line 30 to page 31, line 1 and Feldman *et al.* Ann Rev. Immunol. 14:397-440 (1996).
[17] *Id.* at page 105, lines 3-6.

Treatment of CIA induced mice with mAb 2.3, a CD69 specific antibody that depletes CD69+ cells, significantly reduced CIA.[18] Thus, the antibodies of McInnes 1997 may actually exacerbate rheumatoid arthritis if they do not deplete CD69+ cells. This result was unexpected in light of McInnes 1998, Ledbetter, and McInnes 1997 and also other previously published *in vivo* data. Thus, Applicants submit that the methods of claims 56-60, 67-69 and 105-108 are based on unexpected properties and thus are non-obvious over McInnes 1998, Ledbetter, and McInnes 1997.

The examiner rebuts the Applicants findings of unexpected results by citing McInnes 1998 on page 9 of the Office Action for its teaching that:

> T-cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment, or at least interfere with their membrane interactions, will probably be most efficacious.

While interesting, this teaching is inapposite to the current analysis. Here, McInnes 1998 is suggesting T-cell-directed therapies that not only inhibit T-cell activation but also deplete T cells from the synovial compartment. This is distinct from a method of administering a depleting anti-CD69 antibody such as in the methods now claimed.

The examiner also rebuts the Applicants findings of unexpected results by citing Cheon *et al.* on page 9 of the Office Action for its teaching that:

> TGF-β exerts diverse and even opposite effects depending on the cell types and conditions. In the present study, we provided evidence that TGF-β1 could contribute to the inflammation and progression of the disease in RA and OA.

This passage, while interesting, concerns TGF-β and does not contradict the applicant's unexpected findings that depleting anto-CD69 antibodies show unexpected properties. It appears from the above analysis that the examiner is conflating TGF-β and T-Cells with CD69. TGF-β, T-Cells, and CD69 are all distinct compositions and play a distinct role in any normal or disease physiology.

As explained above, Applicants submit that the Examiner's obviousness rejection is based on an improper obvious to try standard, that there is no motivation to combine McInnes 1998 and Ledbetter or McInnes 1997 and Ledbetter, that there is not a reasonable expectation of

[18] *Id.* at lines 27-29 and Figure 25.

success from the teachings of McInnes 1998, Ledbetter, and McInnes 1997 to successfully arrive at the invention of claims 56, 59, 60, 67-69 and 105-108 and that the methods of claims 56, 59, 60, 67-69 and 105-108 are based on unexpected results. Thus, Applicants submit that claims 56, 59, 60, 67-69 and 105-108 are not obvious over McInnes 1998 in light of Ledbetter, and McInnes 1997, and respectfully requests that this rejection be withdrawn.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicant respectfully submits that this paper is fully responsive and that the pending claims are in condition for allowance. Such action is respectfully requested. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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